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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/333,248	06/15/1999	DEREK VAN DER KOOY	08589/002002	3888

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EXAMINER
LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/333,248	Applicant(s) VAN DER KOOY ET AL.	
	Examiner Gerald Leffers	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/15/99* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/22/02 as Paper No. 14 has been entered.

In Paper No. 14 applicants put forward several arguments for reconsideration of rejection of the pending claims for lack of enablement. Much of the arguments are centered on an evidentiary declaration also submitted on 4/22/02 (Paper No. 13) by one of the inventors, Dr. Vincent Tropepe. These arguments and the declaration have been considered in full, but have not been found to be persuasive for the reasons provided below and for reasons of record.

Information Disclosure Statement

Receipt is acknowledged of an IDS, filed 4/22/02 as Paper No. 11. The signed and initialed PTO Form 1449 has been mailed along with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in Paper No. 8, mailed 4/11/01, and in Paper No. 5, mailed 7/17/00 and repeated below.**

The instant claims are drawn to methods of treating individuals (humans) with a degenerative disease, disorder or abnormal state of the retina or eye (various examples are recited in claim 4) comprising implanting retinal stem cells or retinal cells differentiated from retinal stem cells. The following factors have been considered in the rejection.

The nature of the invention. The nature of the invention is *in vivo* treatment of individuals, especially humans with a wide spectrum of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited to indicate the state of the prior art and the unpredictable nature of the invention. The art at the time of the invention did not recognize retinal stem cells or their use in treatment of degenerative disease, disorder or abnormal physical states of the eye/retina via *in vivo* transplantation. The art does, however, recognize the ability to transplant retinal epithelial cells (RPE cells) (either as a tissue-layer or as individual cells) into the eye of various different animal models, including mammals. RPE cells are one type of cell expected to differentiate from retinal stem cells.

Grisanti et al. (U) teach the transplantation of RPE cells. They teach that normal RPE cells transplanted into the subretinal space of mutant RCS rats survive and rescue photoreceptor cells otherwise destined to undergo degeneration. However, they state that the while these findings are encouraging, the ultimate goal of achieving long-term survival of RPE allografts remains elusive (page 1619). Grisanti et al. also teach that the eye has the rare characteristic of being an immunologically privileged site, but they also caution that the ocular immune privilege

is not absolute and that immunologic recognition of allogenic or xenogenic tissues/cells result in the rejection of histo-incompatible grafts. At page 1625, they teach that even autologous tissue/cells may be rejected if the immune system is not suppressed. They teach that RPE cells produce specific auto-antigens which act as strong immunogens which trigger immune reactions that result in rejection of the RPE cells (see page 1624). They teach that ACAID may have a role as a possible fail-safe mechanism to limit the destructive autoimmune reactions in the privileged sites, but also teach that prolonged ACAID may be accompanied by other detrimental side effects such as fibrosis.

Enzmann et al. (V) teach that while transplantation of RPE cells from embryonic and non-embryonic origins in the subretinal space of different animal models, including the RCS rat has resulted in maintenance of retinal function for long periods of time, such transplantations in humans have yet to be shown to be effective. One reason for this is an immune response to the transplanted cells at the transplantation site. One can detect rejection, indicating that the eye is not absolutely an immunologically privileged site (see for example the abstract). These teachings corroborate those of Grisanti et al. discussed immediately above. At page 182, Enzmann et al. teach that while the immune reaction may be controlled with extensive therapies, transplantation in the subretinal space is performed to improve the quality of life, not to save life. The extensive immunosuppression required may however, endanger the survival of the patient because of its serious side effects. They conclude that many immunological questions must be answered (it is noted that this reference was published two years after Applicant's effective filing date) before extensive efforts in patients are possible and before rejection is no longer a major barrier to success.

Crafoord et al. (W) and Valtink et al. (X), both of which were published in 1999, three years after Applicant's effective filing date, fully corroborate the findings discussed above. They both teach mammalian systems in which strong immunological reactions develop over time

which result in the rejection of the transplanted cells. They both teach that this is a significant hurdle that must be overcome before progress can be made in treating patients with disorders of the retina/eye.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. The specification is completely silent with respect to transplantation of retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE. The specification fails to teach *in vivo* transplantation of any of the above cell types. Because there is no teachings as to how one may achieve transplantation and the fate of the cells after transplantation; the specification also does not teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina, such as those enumerated in claim 4. There are no teachings as to how the skilled artisan would overcome any of the obstacles recognized in the art (summarized above) to reliably and predictably treat any disorder of the eye/retina--especially those as widely varied as blindness (which may a result of optic nerve damage, as opposed to a damaged retina) and cancers of the retina. There is not even a suggestion in either the art or the instant specification as how retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE may treat disorders with a wide variety of etiologies (nerve damage, viral infection, neoplasia, etc.) The teachings of the specification may be characterized as speculative or prophetic at best with regard to treatment of any condition of the eye/retina.

The breadth of the claims. As mentioned above, the claims are drawn to the treatment of any condition of the eye or retina via transplantation of retinal stem cells or cells that have differentiated from said cells.

The quantity of experimentation. The art recognizes several hurdles to successful transplantation of RPE cells to treat degenerative disorders of the retina, including the problems of immunological reactions which result in the rejection of cells that are transplanted into the

eye/retina. The prior art is silent with respect to the transplantation of retinal stem cells, ostensibly because prior to Applicant's disclosure, mammalian retinal stem cells were unknown. Therefore, there is a high degree of unpredictability in the treatment of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. This is especially true for transplantation of retinal stem cells since the art did not recognize this at the time of the invention.

As discussed above, the specification does not provide teachings with regard to the *in vivo* transplantation of retinal stem cells or cells differentiated from retinal stem cells and their fate after transplantation. The specification also fails to teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

In order to practice the invention, the skilled artisan would turn to the prior art and teachings of the specification. However, as summarized in the previous two paragraphs, neither the prior art nor the specification provide teachings which enable the skilled artisan to treat degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. Given the highly unpredictable nature of the invention, the skilled artisan would need to engage in empirical or trial and error experimentation to practice the claimed invention. First the skilled artisan would have to overcome the immune response problem that is well documented in the art, then the artisan would need to establish appropriate transplantation sites, appropriate cell numbers to for each condition found recited in the claims. In addition, the skilled artisan would need to develop appropriate assays to determine which protocols were efficacious (these assays

would certainly vary with the condition to be treated). This level of experimentation would clearly be undue on the part of the skilled artisan and as such, the specification is not found to be enabling for the claimed invention.

Response to Arguments

Applicant's arguments filed in Paper No. 14 have been fully considered but they are not persuasive. The response relies on an evidentiary declaration (Paper No. 13) provided by one of the inventors, Dr. Vincent Tropepe, for its arguments. The response essentially argues: **1)** applicants maintain their arguments presented in Paper No. 7 that the majority of transplant studies using animal models clearly demonstrate the feasibility and success of transplanting embryonic and nonembryonic RPE cells, and that mitigating undesired immune reactions is not a significant barrier when dealing with the transplanted RPE tissue in or near the retina, **2)** the skilled artisan would rely on the teachings of the specification and general knowledge in the art with respect to transplantation of RPE cells into the eye (e.g. Muller-Jensen et al., Mold. Probl. Ophthamol. 15:228-234, 1975; Seigel et al., Cell Transplantation 7:559-566, 1998), **3)** the data provided in the declaration by Dr. Tropepe demonstrate the preparation of retinal stem cells for transplantation using the methods of the invention (e.g. page 20, line 21 to page 23, line 11) and the transplantation of the retinal stem cells and their progeny into the eye using techniques known in the art, **4)** the data provided by Dr. Tropepe demonstrate that some of the transplanted cells differentiated into retinal neurons and that the vast majority of mice injected with the retinal stem cell preparations displayed normal ocular morphology with no evidence of immune rejection after 4 weeks, and **5)** post-filing art by Kurimoti et al (Soc. Neurosci. Abstr., vol. 31,

Program No. 791.11, 2001) demonstrates that retinal stem cell transplants are successful and do not stimulate and adverse immune response.

With regard to arguments made in Paper No. 7 regarding the conclusions that can be made from transplant studies, these arguments were addressed in the previous office action (Paper No. 8). With regard to the Seigel et al reference, it is post-filing art and cannot be relied upon as an indicator of the knowledge of the general art with regard to transplantation techniques for RPE and/or retinal stem cells at the time of filing of the instant specification.

With regard to the data provided by Dr. Tropepe, several factors mitigate against these data demonstrating that the instant specification was enabling at the time of filing. For example, it is not at all clear based upon the art of record that the animal model system used by Dr. Tropepe is art recognized as predictive of success in treating a human animal for any disease, disorder or abnormal physical state of the eye (e.g. those listed in claim 7). Moreover, the only assessment of whether the transplantation of the retinal stem cells in the CD1 mouse resulted in an adverse immune response was a microscopic examination of recipient retinas 4 weeks after transplantation, with no photographic data to support the assertion that no immunogenic response was observable. No data was provided with regard to display of histocompatibility markers on the transplanted cells. Nor is it clear from the art of record or the instant specification that 4 weeks after transplantation in a mouse model is sufficient time in which to conclude that no *long term* immunological response will occur towards the transplanted tissue in the mouse or any other animal. With regard to the differentiation state of the transplanted cells, the photocopies of photographs provided are of poor quality and are difficult to analyze. For example, one cannot assess the co-localization of differentiation markers and the GFP marker to the same cells (as

opposed to merely the same region) based upon these photocopies. Actual photographs would aid in the assessment of the differentiation state of the transplanted cells and would aid in any conclusion with regard to the ability of the transplanted cells to form differentiated cell types in the retina.

Finally, it is not at all clear that the specific methods used by Dr. Tropepe to generate the data were not inventive over what was known in the art at the time of filing. For example, the Muller-Jensen et al reference cited by the response as indicative of the state of the art at the time of filing is directed towards transplantation of RPE cells in owls and rabbits. It is silent with regard to modes of administration of retinal stems cells in the mouse (e.g. the number of cells, the site for injection, means of assaying for immunological reaction, etc.). As noted above, the other reference cited by the response as indicative of the state of the art with regard to transplantation of RPE cells, the Seigel et al reference, is post-filing art. Therefore, based upon the art of record, it is not possible to conclude that the specific methods used by Dr. Tropepe to generate the data provided in his declaration were not inventive in nature (e.g. requiring undue, unpredictable experimentation).

With regard to the teachings of the Kurimoto et al reference, this post-filing reference is merely an abstract that describes the results of retinal transplantation experiments with transgenic mice. No data are presented to support the conclusions recited in the abstract. Little specific detail is provided with regard to the methods used for administering the retinal stem cells, so it is impossible to determine if the methods used by Kurimoto et al are inventive over those taught in the art and instant specification at the time of filing. Moreover, there is no discussion of whether an immune response was detectable after 4 weeks in the retinas of the recipient animals. For at

least these reasons, the Kurimoto et al reference cannot be seen as providing evidence that the rejected claims were enabled by the instant specification at the time of filing.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
July 14, 2002

DAVID GUZO
PRIMARY EXAMINER